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CLASSIC ARTICLE

The pharmacology of cimetidine, a new histamine H_2-receptor antagonist

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Burimamide and metiamide which have been described previously (Black, Duncan, Durant, Ganellin & Parsons, 1972; Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973) are histamine H_2-receptor antagonists. This communication describes some aspects of the pharmacology of cimetidine (N-cyano-N′-methyl-N″ [2-(5- methyl-4-imidazolyl-methylthio)ethyl] guanidine; SK&F 92334), a new H_2-receptor antagonist. *In vitro* the compound antagonizes the actions of histamine on isolated guinea-pig atrium and isolated electrically-stimulated rat uterus with K_B values of 7.9×10^{-7} M and 8.1×10^{-7} M respectively, corresponding to pA_2 values of 6.1 on each tissue. At very high concentrations cimetidine antagonizes the actions of isoprenaline on atrium and uterus and the actions of histamine and carbachol on isolated guinea-pig ileum but the results are not consistent with competitive antagonism at β-adrenoceptors, histamine H_1-receptors or muscarinic receptors.

The effects of cimetidine on gastric acid secretion have been studied in a number of preparations. The results are summarized in Table 1. In all preparations cimetidine was approximately equiactive in inhibiting histamine and pentagastrin-stimulated acid secretion but less effective in inhibiting carbachol-stimulated secretion. Basal secretion was also inhibited. In Heidenhain pouch dogs the blood levels to give 50% inhibition of maximally-stimulated gastric secretion (EC50) were

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Table 1 The effects of cimetidine on gastric acid secretion

Preparation	*Stimulant*	*Effect of Cimetidine*
Rat: Lumen-perfused stomach	Histamine 15 μmol kg^{-1} h^{-1}	ID50 (rapid i.v. injection) 1.37 μmol/kg ID50 (intraduodenal administration) 5.5 μmol/kg i.v. infusion of 3 μmol kg^{-1} h^{-1} produced mean inhibition of 71%
	Pentagastrin 60 μg kg^{-1} h^{-1}	ID 50 (rapid i.v. injection) 1.4 μmol/kg
	Carbachol 30 μg kg^{-1} h^{-1}	Variable effect. Significant inhibition at 8 μmol/kg Approximately 50% inhibition at 128–256 μmol/kg
Rat: Gastric fistula	Basal secretion	i.v. infusion of 6 μmol kg^{-1} h^{-1} produced mean inhibition of 20% in first hour and 30% in second hour. With 60 μmol kg^{-1} h^{-1} inhibitions were 71% and 96% respectively.
Cat: Lumen-perfused stomach	Histamine 3 μmol kg^{-1} h^{-1}	ID50 (rapid i.v. injection) 0.85 μmol/kg
	Pentagastrin 10 μg kg^{-1} h^{-1}	ID50 (rapid i.v. injection) 1.45 μmol/kg
Dog: Heidenhain pouch	Histamine 1.3 μmol kg^{-1} h^{-1}	ID50 (rapid i.v. injection) 1.7 μmol/kg IE50 (i.v. infusion) 4.7 μmol kg^{-1} h^{-1} Oral administration of 10 & 20 μmol/kg produced mean inhibitions of 70 & 90% respectively
Dog: Heidenhain pouch	Pentagrastrin 8 μg kg^{-1} h^{-1}	2 μmol/kg by rapid i.v. injection gave mean inhibition of 55%
	Carbachol 6.7 μg kg^{-1} h^{-1}	4 μmol/kg by rapid i.v. injection gave mean inhibition of 59%

approximately 1–2 μM and the half-life of the compound about one hour.

In male human volunteers cimetidine given intravenously has been shown to inhibit histamineor pentagastrin-stimulated gastric secretion with an EC50 of about 2.5 μM and a half-life of about two hours.

In chronic toxicity studies metiamide has been shown at high doses to produce kidney damage and agranulocytosis in some dogs (Brimblecombe, Duncan & Walker, 1973). In tests so far carried out cimetidine at equivalent doses has not shown similar toxicity.

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